

AMENDMENT TO THE SPECIFICATION

Please amend paragraph [0100] starting on page 24, line 23 as follows:

Examples I-XI disclosed in this invention illustrate various methods useful for the following purposes: (a) Induction of synthesis of Abs that can bind covalently and specifically with the target polypeptide antigen; (b) Induction of synthesis of Abs that can specifically catalyze the hydrolysis of various target polypeptide antigens; (c) Isolation of specific covalent and catalytic Abs from the natural Ab repertoire expressed in patients with autoimmune disease; (d) Permanent inactivation of pathogenic catalytic Abs expressed by patients with autoimmune disease; (e) Use of transonic mice with dysfunctional B cell transmembrane as hosts to raise catalytic Abs; and (f) Use of ~~transgenic transonic~~ mice expressing the human Ab genes to raise human covalent and catalytic Abs.

Please amend paragraph [0103] starting on page 25, line 9, as follows:

In another aspect of the invention, the pCRAs and pCRAWs are applied for isolation of therapeutic Abs, for example by: (a) preparing monoclonal Abs from ordinary mice and ~~transgenic transonic~~ mice expressing the human Ab repertoire; (b) chemical selection of the desired antibodies from autoimmune phage display libraries; and (c) directed evolution of the Abs in vitro. In each case, efficient methods for screening and selection are applied to permit isolation of rare Abs with the desired activities. The covalent and catalytic Abs so generated would then be administered to patients to inactivate targeted antigen moieties. In this scenario, should the patient experience adverse side effects, the immunizing pCRA or pCRAW maybe administered to irreversibly inactivate the catalytic antibody.

Please amend paragraph [0486] starting on page 90, line 4, as follows:

He, Y., Honnen, W. J., Krachmarov, C. P., Burkhart, M., Kayman, S. C., Corvalan, J., and Pinter, A. (2002). Efficient isolation of novel human monoclonal antibodies with neutralizing activity against HIV-1 from ~~transgenic transonic~~ mice expressing human Ig loci. J. Immunol. 169, 595-605.

Please amend paragraph [0559] starting on page 100, line 18, as follows:

Individual VH domains from Abs with established gp120-recognizing activity, e.g., antibody clones S1-1 (15) or b12 (16) can be employed as the lupus VL domains partners. Alternatively a library of VH domains is employed to increase the probability of finding appropriate VH domains capable of forming a compatible V.sub.L-V.sub.H molecular interface (i.e., an interface that brings the CDRs into sufficient spatial proximity to form a functional catalytic site). The most favorably paired V.sub.L-V.sub.H domains are then identified by phage selection methods even if they constitute a minority of the overall combinations. Suitable V.sub.H domain sources are the HIV-1 infected individuals, who produce large amounts of specific anti-gp120 antibodies. Another suitable source of VH domains is transonic mice expressing human antibodies that are immunized with gp120 or synthetic gp120(421-436), e.g., XenomouseTM mice produced by Abgenix Inc. Methods for immunization of these mice are as described by us previously (17), by administration of gp120 or synthetic gp120(421-436) conjugated to carrier

proteins. Preparation of scFv libraries from the HIV-infected individuals and the ~~transgenic transgenic~~ mice is essentially as described previously (18). Phages expressing scFv are subjected to selection by binding to gp120 or synthetic gp120(421-436) as before, allowing recovery of scFv clones as the source of VH domains. A large proportion of V.sub.H domains from these scFv clones can be anticipated to independently recognize gp120, as suggested by studies that the V.sub.H domain provides a dominant contribution in noncovalent antigen recognition. Such VH domains are suitable as partners for the anti-HIV L chains isolated from lupus patients.

Please amend paragraph [0560] starting on page 100, line 34, as follows:

Methods to generate the hybrid scFvs are in place in our lab (18). Essentially, the cDNA of the V.sub.L cDNA is amplified from the vector using primers containing the appropriate restriction sites necessary for cloning into pHEN2 vector containing the scFv constructs. The linker sequence is contained within the vector. Following removal of the endogenous V.sub.L domain cDNA by restriction digestion, the desired V.sub.L domain is ligated into the vector. VH domains from phage DNA selected as in the preceding paragraph (from HIV-1 infected individuals and ~~transgenic transgenic~~ mice) are then ligated into the vector, and hybrid scFv phages will be packaged. The hybrid phages expressing hybrid scFv are subjected to CRA selection and screening for cleavage of the appropriate gp120 antigenic preparation. The success of this strategy is reflected by increased gp120 cleaving activity and HIV-1 neutralizing activity of the scFv clones compared to the parental L chain.

Please amend paragraph [0560] starting on page 100, line 34, as follows:

Murine MAbs are not ideal for passive immunotherapy (because of possible anti-Ab responses). However, the methods developed in the present aim are readily applicable to obtain human Abs from transgenic ~~transgenic~~ mice expressing the human Ab locus (10). These mice are shown to mount robust and high affinity human Ab responses to a variety of antigens. Similarly, SCID mice reconstituted with human lymphocytes can mount human Ab responses. Finally, molecular engineering techniques are available to humanize murine Abs, consisting of grafting the murine V domains into the constant domain scaffold of a human Ab, followed by replacements in the murine V domains that reduce human anti-mouse Ig responses. Guided by molecular modeling or crystal structures, the antigen contacting residues are maintained. Thus, there is no insurmountable difficulty in obtaining human and humanized proteolytic Abs to A.beta. peptide.